Cardiology in the Young

cambridge.org/cty

Evaluation of subclinical atherosclerosis and cardiac functions in children of mothers with gestational diabetes and maternal obesity

Melda Ekici Avci[1] and Öykü Tosun[2]

[1]Department of Pediatrics, Istanbul Medeniyet University, Göztepe Profesör Doktor Süleyman Yalçın City Hospital, Istanbul, Turkey and [2]Department of Pediatric Cardiology, Istanbul Medeniyet University, Göztepe Profesör Doktor Süleyman Yalçın City Hospital, Istanbul, Turkey

Original Article

Cite this article: Ekici Avci M and Tosun Ö (2023) Evaluation of subclinical atherosclerosis and cardiac functions in children of mothers with gestational diabetes and maternal obesity. *Cardiology in the Young* **33**: 1157–1164. doi: 10.1017/S1047951122002402

Received: 29 November 2021
Revised: 26 June 2022
Accepted: 5 July 2022
First published online: 29 July 2022

Keywords:
Arterial compliance; carotid intima-media thickness; epicardial adipose tissue thickness; gestational diabetes; maternal obesity; socio-economic status

Author for correspondence:
Melda E. Avci, Department of Pediatrics, Istanbul Medeniyet University, Göztepe Profesör Doktor Süleyman Yalçın City Hospital, Fahrettin Kerim Gökay Caddesi, 34722, Kadıköy/İstanbul, Turkey.
Tel: +491772747514; Fax: +902166065210.
E-mail: dr.melda.eavci@gmail.com

Abstract

Background and aims: We aimed to evaluate the effects of maternal obesity or gestational diabetes on body composition, lipid, and glucose metabolism, arterial morphology, and functions in children, and to investigate these effects in terms of cardiometabolic diseases. *Methods:* The study group was composed of 48 children who had a history of gestational diabetes or maternal obesity, and the control group was composed of 33 children. Echocardiographic assessments were performed. Socio-economic status and education level of mothers were obtained. *Results:* In the study group, carotid intima-media thickness, epicardial adipose tissue thickness, and arterial stiffness values were found to be significantly higher compared to the control group ($p < 0.001$, $p < 0.001$, $p = 0.003$, respectively), while arterial distensibility and arterial strain values were found to be significantly lower ($p = 0.003$, $p = 0.008$, respectively). Among the children who had similar body mass index in both groups, children in the study group had higher carotid intima-media thickness and epicardial adipose tissue thickness values. Arterial stiffness values were significantly reduced ($p = 0.028$) and arterial distensibility and strain values were significantly increased ($p = 0.039$, $p = 0.033$, respectively) in the children whose mothers had gestational diabetes and high socio-economic status. Left ventricular mass and left ventricular end-diastolic internal thickness were found to be significantly increased in the children who had obese and unemployed mothers ($p = 0.04$, $p = 0.03$, respectively). *Conclusion:* Low socio-economic status was found to be associated with increased maternal obesity and gestational diabetes. Poor socio-economic status, poor glycaemic control and being overweight during pregnancy indicate negative cardiometabolic outcomes for children in the long term.

Cardiovascular diseases continue to be the leading cause of morbidity and mortality globally, though a significant improvement has been achieved in the last decade. The most important factor in the pathophysiology of cardiovascular disease is atherosclerosis. Although atherosclerosis is clinically observed at adult ages, it subclinically begins with fatty streaks in the arterial intima layer in early childhood and predisposes to the development of cardiovascular diseases in adulthood. It is thought that nutritional and environmental factors in the intrauterine life have permanent effects on children in terms of metabolic and neurological development, and this is also known as the fetal programming hypothesis.[1] Gestational diabetes mellitus and maternal obesity influence cardiometabolic development in children beginning from the intrauterine period.[1–3] Inflammation caused by hyperglycaemia, insulin resistance, and increased adipose tissue which develops in presence of maternal obesity and gestational diabetes mellitus, is thought to influence cardiovascular health in children.[1–3] It is possible to calculate carotid intima-media thickness, epicardial adipose tissue thickness, diameter changes during systole and diastole, and parameters such as arterial stiffness and elasticity with echocardiographic examination. These parameters that give information about subclinical atherosclerosis in children provide a prediction about the risk of cardiovascular disease at advanced ages.[4,5] There is evidence indicating that these parameters are influenced by maternal obesity or the presence of gestational diabetes mellitus.[2,5–7] In this study, we aimed to investigate the long-term effects of the presence of maternal obesity or gestational diabetes mellitus, and families' socio-economical status in children, such as subclinical atherosclerosis, cardiac functions, metabolic syndrome, insulin resistance, and dyslipidemia.

Materials and methods

This study was conducted prospectively at Istanbul Medeniyet University Prof. Dr Süleyman Yalçın Göztepe City Hospital Pediatric Cardiology Outpatient Clinics between July, 2019 and December, 2020. Our hospital's local ethics committee approved this study with the report

number 2019/0312. The study was conducted in accordance with the Helsinki Declaration, and written informed consent was obtained from the parents in the study and control groups.

Study population

Forty-eight healthy children aged between 3 and 12 years who had a history of gestational diabetes mellitus (specified by interrogating a diagnosis of gestational diabetes mellitus and oral glucose tolerance test during pregnancy) or maternal obesity[8] (gestational body mass index ≥ 30 kg/m^2, body weight >91 kg or above normal body weight by 110–120%) were included in the study group (27 children whose mothers had obesity and 21 children whose mothers had gestational diabetes mellitus). Thirty-three healthy children aged between 3 and 12 years who had no history of gestational diabetes mellitus or maternal obesity were included in the control group. The age of 3–12 years range was considered as the borderline due to the fact that atherosclerotic lesions begin to be observed from the age of 3 years, to eliminate the effects of pubertal hormonal changes. Children who had systemic chronic morbidity, congenital/acquired heart and valve disease, and pathological ECG and echocardiographic findings were excluded from the study and control groups. During history taking, gestational age, birth weights, periods of breastfeeding, time of starting solid foods, maternal working status, maternal occupation, maternal education level, home income, consanguineous marriage, smoking status, presence of chronic disease, gestational body weight, folic acid supplement, and physical activity during pregnancy were interrogated. To inspect to potential effects of the gestational age of participants on this work, whole participants were classified as "preterm" (birth week<37) or "term" (birth week ≥ 37) based on their birth week. The difference between subclinical atherosclerosis parameters was evaluated in these two groups.

Anthropometric measurements

The childrens' body weights and heights in the study and control groups were measured using digital scales and stadiometer, and height and weight percentiles by age and sex were evaluated using standard growth charts specified for our country.[9] Body mass index was calculated by dividing body weight (kg) by the square of height (m^2). A body mass index value of ≥ 95th percentile according to the growth charts specified for Turkish children was considered obesity.[9] Wrist circumference, mid-upper arm circumference, and waist circumference were measured using a standard non-elastic tape measure. The children were put in the upright position with their abdomens set free, waist circumference was measured over the umbilicus, and mid-upper arm circumference was measured over the middle points between the shoulder and elbow with the elbow at 90 degrees flexion, and wrist circumference was measured with the wrist, radius and ulna in the upright position with the long axis of the forearm distal to the styloid processes using a standard non-elastic tape measure. These measurements were recorded in cm.

Blood pressure and biochemical markers

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured on an empty stomach in the sitting position following a 15-minute rest period over the right brachial artery using an oscillometer (Omron M2) and cuffs of appropriate size. Hypertension criteria according to the American Academy of Pediatrics were specified.[10] Prior blood glucose, insulin, lipid profiles (high-density lipoprotein, low-density lipoprotein, total cholesterol, and triglyceride), free triiodothyronine (fT3), free thyroxine (fT4), and thyroid-stimulating hormone of the patients, which were learned to be measured following a 12-hour fasting period, were included in the study. A homeostatic model assessment of insulin resistance value of > 2.5 was considered insülin resistance. Dyslipidemia criteria were specified as follows: total cholesterol ≥ 200 mg/dl, low-density lipoprotein ≥ 130 mg/dl, triglyceride 0–9 years ≥ 100, 10–19 years ≥ 130 mg/dl, high-density lipoprotein < 40 mg/dl.[11] The criteria for metabolic syndrome were specified according to the International Diabetes Federation (IDF).[12] Subclinical hypothyroidism was defined as increased thyroid-stimulating hormone in the presence of normal free FT4 concentrations.[13]

Echocardiography

The echocardiographic assessment was performed in a single-blind manner using Philips Epic 7C device and S5–1 and S8–3 linear probe with standard position and techniques. Left ventricular end-diastolic internal thickness, interventricular septum systolic thickness, interventricular septum diastolic thickness, left ventricular posterior wall systolic thickness, and left ventricular posterior wall diastolic thickness were measured and fractional shortening, ejection fraction, and left ventricular mass (LVM) were calculated digitally. The LVM index (LVMI) was calculated using the formula: LVMI = LVM/Height$^{2.7}$ and percentiles were examined based on the age.[14] Epicardial adipose tissue thickness was measured vertical from the hypoechoic area adjacent to the right ventricular free wall to the right ventricular wall in the parasternal long-axis view. The maximum values were considered, and the mean value was reported. Carotid intima-media thickness assessment and specification of the carotid layers were performed according to the American Echocardiography Association standard protocol.[15] A probe was placed along a vascular axis to obtain a longitudinal scan of the right main coronary artery with the patient in the supine position and the head slightly turned to the left. Carotid intima-media thickness measurement was performed 1 cm proximal to the carotid artery bifurcation. The average value of three cardiac cycle measurements was recorded. Carotid artery systolic diameter (Ds) and diastolic diameter (Dd) were measured, and the parameters including arterial distensibility, stiffness, and strain were calculated using the following methods[16]:

Arterial Strain = (Ds – Dd)/Dd

Arterial Distensibility (cm^2.dyn-1) = 2x (Ds – Dd)/(Dd x pulse pressure)

Arterial Stiffness (mmHg) = (SBP/DBP)/strain

Statistical analysis

SPSS 24 (Statistical Package for Social Science, version 24) and Python 3.9 (scipy) were used for statistical analysis. Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as numbers and percentages. Mann–Whitney U-test was used in the comparison of two groups for the variables that did not show a normal distribution (Supplementary Table S2), and the Kruskal–Wallis test was used in the comparison of three or more samples groups (Tables 1 and 2). The Chi-square test was used in the comparison of qualitative data (Table 1, Supplementary Table S1). Spearman's correlation analysis was used for the examination of the relationship between variables. Based on the correlation analysis results, the

https://doi.org/10.1017/S1047951122002402 Published online by Cambridge University Press

Table 1. Clinical and charactheristical profile of groups

		Maternal obesity		GDM		Control group		
		n	%	n	%	n	%	p[a]
Sex	Male	10	37.04	10	47.6	20	60.6	0.189[b]
	Female	17	62.96	11	52.4	13	39.4	
Age (month)		89 ± 28.75		102.3 ± 36.1		105.15 ± 28.87		0.083[a]
Height (cm)		128 ± 17.2		131.8 ± 18.75		134.5 ± 15.5		0.278[a]
Weight (kg)		34.8 ± 14.8		33.7 ± 13.3		32.65 ± 11.05		0.968[a]
BMI (kg/m^2)		20.7 ± 4.3		18.8 ± 4.06		17.75 ± 3.5		**0.013**[a]
WC (cm)		71.2 ± 14.6		68.6 ± 12.9		66.05 ± 9.4		0.456[a]
MUAC(cm)		23.3 ± 3.9		22.3 ± 4.3		21.45 ± 3.6		0.193[a]
WrC (cm)		15.15 ± 1.7		14.7 ± 1.35		14.5 ± 1.3		0.42[a]
Breastfeeding duration (months)		15.2 ± 9.7		17.7 ± 9.6		17.4 ± 13.2		0.507[a]
Birth weight (g)		3089.4 ± 975.5		3141.4 ± 696.5		3123.6 ± 545		0.865[a]
Gestational age	Preterm	3	11	4	19	7	21	
	Term	24	89	17	81	26	79	
Time of introducing complementary feeding		6.5 ± 1.6		6.05 ± 1.02		5.9 ± 0.55		0.089[a]
Systolic blood pressure (mmHg)		99.6 ± 15.7		98.9 ± 15.75		104.4 ± 9.9		0.24[a]
Diastolic blood pressure (mmHg)		60.8 ± 14		61.2 ± 14		69.3 ± 8.5		**0.035**[a]
Insulin resistance	Resistant	5	18	7	33	0	0	
	Non-resistant	22	82	14	67	33	100	
LVMI$^{2.7}$ (g/m$^{2.7}$)	>%95 percentile	5	18	5	23	1	3	
	<%95 percentile	22	82	16	77	32	97	

Values are presented as n (mean+SDS).
BMI = body mass index; GDM = gestational diabetes mellitus; LVMI = left ventricular mass index; MUAC = mid-upper arm circumference; WC = waist circumference; WrC = wrist circumference.
[a]Kruskal–Wallis test.
[b]Chi-square test.
$p < 0.05$ compared with reference population.

data were visualised with a scatter plot chart (Fig 1). A p-value of <0.05 was considered statistically significant. Receiver operating characteristic was performed to determine the most sensitive and specific parameter for subclinical atherosclerosis (Fig 2). Multiple regression analysis was conducted to inspect the potential effect of confounding factors. A post hoc sample size calculation was made due to the relatively small sample size.

Results

The demographic and anthropometric properties belonging to the study and control groups are shown in Table 1. The groups did not show a difference in terms of mean values for age (months), sex, height, and weight. Body mass index was found to be significantly higher in the study group compared to the control group ($p = 0.013$). Although the mean values for waist, arm, and wrist circumference were found to be higher in the study group compared to the control group, the differences were not statistically significant. No hypertensive subject was found in the groups. Even though SBP did not show a difference between the groups, DBP was found to be significantly increased in the control group ($p = 0.035$). Thyroid-stimulating hormone, FT3, and triglyceride levels were found to be significantly increased ($p = 0.002$, $p < 0.001$, $p = 0.026$, respectively), and high-density lipoprotein levels were found to be significantly reduced ($p = 0.028$) in the study group (Table 2). There was no case with clinical or subclinical hypothyroidism among participants. Insulin resistance and increased triglyceride levels were found in five of the children who had maternal obesity and in seven of the children whose mothers had gestational diabetes. Abnormal laboratory finding was not observed in the control group. Metabolic syndrome was observed in one child with maternal obesity.

The echocardiographic data belonging to the groups are shown in Table 2. Carotid intima-media thickness and epicardial adipose tissue thickness were found to be significantly high in the study group ($p < 0.001$ for both parameters). Arterial stiffness was found to be significantly increased ($p = 0.003$), and arterial strain and distensibility were found to be significantly reduced ($p = 0.008$, $p = 0.003$, respectively) in the study group. Aortic peak wave velocity, left ventricular mass, and conventional echocardiographic parameters did not show a difference between the groups. Left ventricular mass index was found to be higher than the 95th percentile for age in five cases with maternal obesity, with a history of gestational diabetes mellitus, and in one case in the control group.

The relationship between the childrens' body compositions and echocardiographic parameters was evaluated. A positive correlation was found between left ventricular mass and body mass index

https://doi.org/10.1017/S1047951122002402 Published online by Cambridge University Press

Table 2. Comparison of laboratory and echocardiographic findings in study and control groups

	Maternal obesity (n=27)	GDM (n=21)	Control group (n=33)	
	Mean+SDS	Mean+SDS	Mean+SDS	p
Glucose (mg/dl)	86.9 ± 8.9	84.9 ± 8.4	86.9 ± 8.6	0.536
Insulin (uU/ml)	8.2 ± 6.9	10.5 ± 9.1	6.35 ± 2.7	0.275
HOMA-IR	1.8 ± 1.4	2.17 ± 1.8	1.4 ± 0.6	0.316
TSH (uIU/ml)	2.04 ± 0.7	2.2 ± 1	1.5 ± 0.6	**0.002**
FT4 (ng/dl)	1.02 ± 0.1	0.96 ± 0.1	1.1 ± 0.6	0.281
FT3 (pg/ml)	4.2 ± 0.5	4.1 ± 0.6	3.7 ± 0.6	**<0.001**
HDL (mg/dl)	56.5 ± 12.5	50.9 ± 11.7	60.8 ± 13.5	**0.028**
LDL (mg/dl)	92.9 ± 26.3	79.7 ± 22	87.3 ± 20.4	0.147
Total cholesterol (mg/dl)	169.7 ± 28.8	155.7 ± 28.5	162.7 ± 23.6	0.179
Triglycerides (mg/dl)	107.8 ± 75.4	125.2 ± 86.6	68.8 ± 21.2	**0.026**
Aortic PWV (cm/sn)	108.46 ± 20	104.93 ± 16.2	107.28 ± 19.7	0.856
LV mass (g)	66.74 ± 28.1	67.84 ± 24.3	67.29 ± 19.24	0.805
$LVMI^{2.7}$ ($g/m^{2.7}$)	33.6 ± 8.45	33.51 ± 8.3	30.75 ± 8.5	0.39
EATT (mm)	4.68 ± 1.16	4.3 ± 1.14	2.77 ± 1.3	**<0.001**
CIMT (mm)	1.12 ± 0.34	1.1 ± 0.33	0.79 ± 0.16	**<0.001**
Arterial distensibility (cm^2.dyn-1)	0.0097 ± 0.007	0.01 ± 0.01	0.014 ± 0.007	**0.003**
Arterial strain	0.19 ± 0.15	0.17 ± 0.12	0.26 ± 0.12	**0.008**
Arterial stiffness (mmHg)	15.87 ± 14.35	17.86 ± 14.9	7.48 ± 4.26	**0.003**

Values are presented as mean+SDS.
$p < 0.05$ is accepted as significant.
Aortik PWV = aortic peak wave velocity; CIMT = carotid intima-media thickness; EATT = epicardial adipose tissue thickness; GDM = gestational diabetes mellitus; FT3 = free triiodotironin; FT4 = free tyroxine; HDL = high-density lipoprotein; HOMA-IR = homeostatic model assessment of insulin resistance; LDL = low-density lipoprotein; LV mass = left ventricular mass; LVMI = left ventricular mass index; TSH = thyroid-stimulating hormone.
$p < 0.05$ compared with reference population.

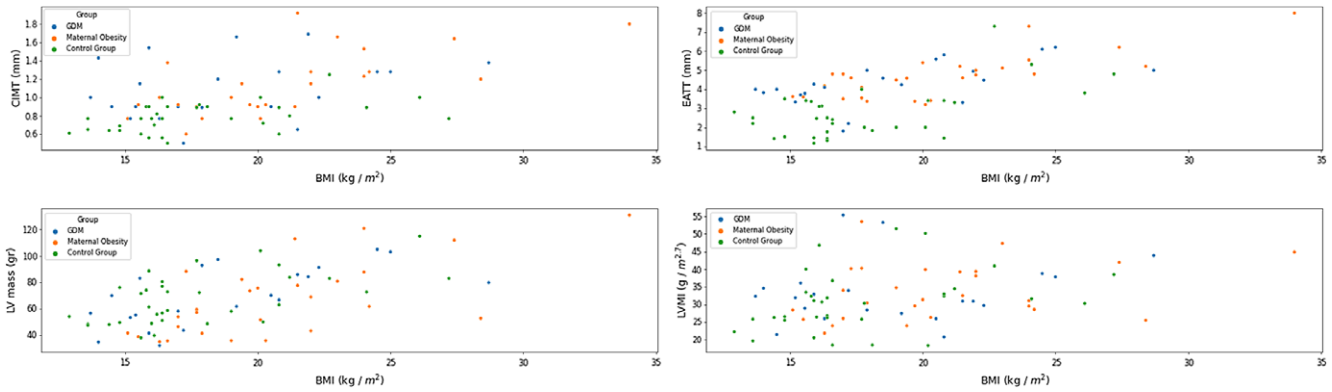
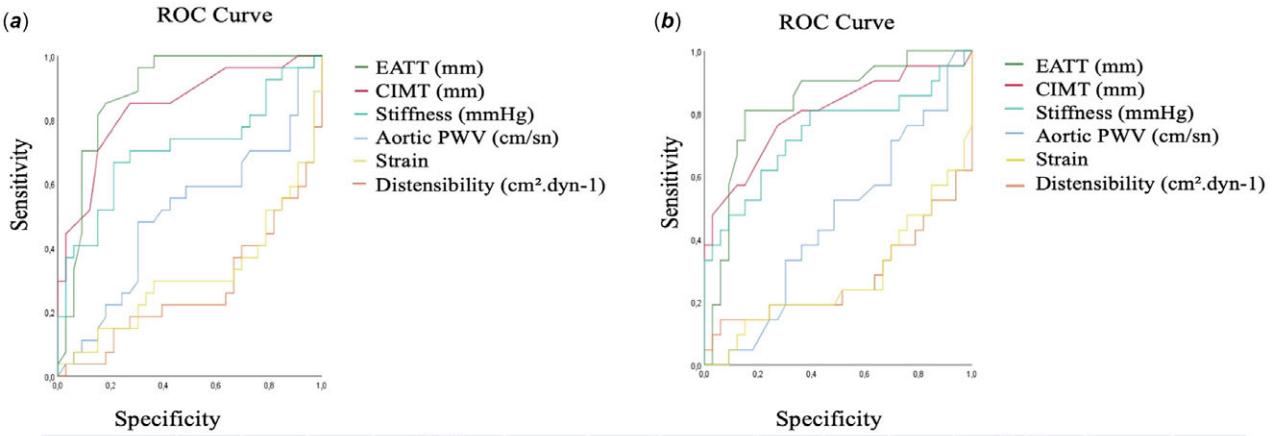


Figure 1. Relationship and distribution of CIMT, EATT, LV Mass and LVMI with BMI in all groups.

($p = 0.001$, $r = 0.6$), waist circumference ($p < 0.001$, $r = 0.698$), mid-upper arm circumference ($p < 0.001$, $r = 0.698$), wrist circumference ($p < 0.001$, $r = 0.828$), between epicardial adipose tissue thickness and body mass index ($p < 0.001$, $r = 0.631$), waist circumference ($p < 0.001$, $r = 0.693$), mid-upper arm circumference ($p < 0.001$, $r = 0.629$), WrC ($p < 0.001$, $r = 0.624$) and between carotid intima-media thickness and body mass index ($p = 0.001$, $r = 0.612$), waist circumference ($p = 0.002$, $r = 0.575$), mid-upper arm circumference ($p = 0.003$, $r = 0.557$), and wrist circumference ($p = 0.023$, $r = 0.437$) in the children with maternal obesity. In the children whose mothers had gestational diabetes mellitus, a positive correlation was found between left ventricular mass and body mass index ($p = 0.005$, $r = 0.587$), waist circumference ($p = 0.003$, $r = 0.611$), mid-upper arm circumference ($p = 0.008$, $r = 0.562$), wrist circumference ($p = 0.011$, $r = 0.542$), and between epicardial adipose tissue thickness and body mass index ($p = 0.002$, $r = 0.637$), waist circumference ($p = 0.001$, $r = 0.659$), mid-upper arm circumference ($p = 0.003$, $r = 0.622$), and wrist circumference ($p = 0.005$, $r = 0.593$). A negative correlation was found between waist circumference measurements and arterial distensibility

https://doi.org/10.1017/S1047951122002402 Published online by Cambridge University Press



Maternal Obesity	Cut off	AUC	p	95% CI Lower Bound	95% CI Upper Bound	Sensitivity	Specifity	GDM	Cut off	AUC	p	95% CI Lower Bound	95% CI Upper Bound	Sensitivity	Specifity
Aortik PWV (cm/sn)		0.506	0.941	0.354	0.657			Aortik PWV (cm/sn)		0.542	0.607	0.385	0.698		
CIMT (mm)	>0.895	0.842	**<0.001**	0.74	0.944	85.19	63.64	CIMT (mm)	>0.895	0.802	**<0.001**	0.672	0.931	76.19	72.73
EATT (mm)	>3.45	0.887	**<0.001**	0.8	0.975	85.19	81.82	EATT (mm)	>3.6	0.836	**<0.001**	0.722	0.95	80.95	84.85
Arterial Distensibility (cm².dyn-1)	<0.011	0.726	**0.003**	0.593	0.859	77.78	63.64	Arterial Distensibility (cm².dyn-1)	<0.009	0.723	**0.006**	0.566	0.88	61.9	78.79
Arterial strain	<0.18	0.686	**0.014**	0.543	0.828	62.96	75.76	Arterial strain	<0.021	0.722	**0.006**	0.572	0.871	76.19	66.67
Arterial Stiffness (mmHg)	>7.692	0.71	**0.005**	0.572	0.849	70.37	69.7	Arterial Stiffness (mmHg)	>0.659	0.737	**0.004**	0.589	0.886	80.95	60.61

Figure 2. ROC analysis for subclinical atherosclerosis parameters of the study group.

($p = 0.04$ $r = -0.451$) and arterial strain ($p = 0.047$ $r = -0.439$) values.

Although carotid intima-media thickness, epicardial adipose tissue thickness, left ventricular mass, and left ventricular mass index were correlated with body mass index, it was observed that the study group showed a distribution of significantly increased values compared to the control group in the same body mass index value range (Fig 1).

The effects of preterm and term birth on subclinical atherosclerosis parameters were examined. The mean of the birth week parameter was 33.8 ± 2.27 in the study and control groups, and 39.27 ± 0.76 in those born at term. When these two groups were compared in terms of subclinical atherosclerosis parameters, no significant difference was found for the parameters carotid intima-media thickness, epicardial adipose tissue thickness, arterial stiffness, arterial distensibility, arterial strain, and left ventricular mass, but a significant difference was determined for left ventricular mass index ($p = 0.36$, $p = 0.52$, $p = 0.69$, $p = 0.62$, $p = 0.63$, $p = 0.31$, $p = 0.002$, respectively). In the correlation analysis conducted for the same parameters, no significant correlation was observed except for left ventricular mass index.

To investigate the effect of confounding factors, multiple regression analysis was performed between subclinical atherosclerosis parameters and gender, age, body mass index, low-density lipoprotein, high-density lipoprotein, homeostatic model assessment of insulin resistance , thyroid-stimulating hormone, and SBP in the study groups. Body mass index was determined as a significant predictor for carotid intima-media thickness and epicardial adipose tissue thickness ($p = 0.041$, $p = 0.003$) and age for left ventricular mass in children with maternal obesity ($p = 0.003$). Gender was a predictive factor for epicardial adipose tissue thickness in children of mothers with gestational diabetes mellitus ($p = 0.04$).

Maternal characteristics are shown in Supplementary Table S1. Education level was found to be lower in the study group compared to the control group (for maternal obesity $p = 0.02$, for gestational diabetes mellitus $p = 0.046$). The number of mothers who practiced exercise during pregnancy was found to be significantly higher in the study group (for maternal obesity $p = 0.028$, for gestational diabetes mellitus $p = 0.018$).

Supplementary Table S2 shows the relationship between socioeconomical status and subclinical atherosclerosis, left ventricular structure, and left ventricular functions. Carotid systolic diameter, diastolic diameter, and carotid intima-media thickness were found to be significantly higher in the children whose mothers had obesity and chronic morbidity compared to the children whose mothers did not have a history of chronic morbidity ($p = 0.02$, $p = 0.03$, $p = 0.03$, respectively). The children whose mothers had gestational diabetes mellitus with a monthly family income above 4000 tl had higher carotid artery distensibility and strain values and lower arterial stiffness compared to the ones with a monthly family income below 4000 tl ($p = 0.039$, $p = 0.033$, $p = 0.028$, respectively).

Receiver operating characteristic analysis was performed to determine the most sensitive and the most specific parameter indicating subclinical atherosclerosis in children in presence of maternal obesity and gestational diabetes mellitus. Epicardial adipose tissue thickness was determined the most sensitive (85.1, 80.9%, respectively) and the most specific (81.8, 84.8%, respectively) parameter both for the maternal obesity and gestational diabetes mellitus group (Fig 2).

Discussion

Maternal hyperglycaemia resulting from gestational diabetes mellitus and maternal obesity causes fetal hyperglycaemia and leads to

https://doi.org/10.1017/S1047951122002402 Published online by Cambridge University Press

fetal hyperinsulinemia. Hyperinsulinemia increases the risk for obesity at advanced ages by increasing fetal adipose mass.[1–3] The finding that body mass index was higher in the study group compared to the control group was considered an outcome of this process. Body mass index is insufficient to give adequate information about body fat distribution. Therefore, anthropometric measurements are used for this objective. Although the mean values for waist circumference, mid-upper arm circumference, and wrist circumference measurements in the study group in our study were found to be higher compared to the control group and the difference was not statistically significant, various studies showed the effects of maternal diabetes on adipose mass and fat distribution in children.[17] In addition, studies showed that insulin with its anabolic effects contributed to bone remodelling and bone development by causing increased osteoblastic activity, and wrist circumference measurement was a good marker for this.[18] Therefore it has been determined that hyperglycaemia and hyperinsulinemia have negative effects on fat distribution and body composition by causing faulty metabolic programming from fetal life. SBP did not show a difference between the groups, while DBP was found to be increased in the control group. Studies have shown different results about the effect of gestational diabetes mellitus and maternal obesity on blood pressure in children.[5–7,19]In healthy children, blood pressure is correlated with height and age.[20] Our study had a wide age and height range for the assessment of blood pressure. Thus, we think that subjects with the same age and height range should be compared to investigate the effects of the presence of gestational diabetes and maternal obesity on blood pressure.

In studies conducted with euthyroid and obese individuals, thyroid-stimulating hormone and FT3 levels were found to be increased,[21] while results for FT4 showed a difference.[21,22] In our study, no case with subclinical hypothyroidism was detected, but only significantly higher thyroid-stimulating hormone levels were associated with increased body mass index, similar to the studies performed. Maternal obesity or gestational diabetes mellitus is thought to lead to an increase in body mass index in children and thus an increase in thyroid-stimulating hormone levels.

In presence of atherosclerosis-related risk factors, thickening and damage in the arterial intima-media layer begin at an early age.[2,4,23] Increased epicardial adipose tissue thickness and carotid intima-media thickness in presence of gestational diabetes mellitus or maternal obesity in our study showed the negative effect of prenatal risk factors involved in the development of atherosclerosis in children. Studies have shown that epicardial adipose tissue thickness is increased in children of mothers with gestational diabetes mellitus or pregestational obesity both in fetal life and later in childhood.[24,25] Epicardial adipose tissue thickness is a visceral adipose tissue with paracrine, vasocrine, and inflammatory functions localised around the heart and coronary arteries and is influenced by body fat distribution.[5,24,25] Although the relationship between the children's body compositions and body mass index and epicardial adipose tissue thickness and carotid intima-media thickness shows that these parameters increase the risk for cardiovascular disease with increased obesity, the fact that the study group had higher carotid intima-media thickness and epicardial adipose tissue thickness values compared to the control group in the same body mass index range, as shown in Figure 1, indicated the influence of maternal gestational diabetes mellitus and gestational obesity independent of children's body mass index. Even though body mass index was correlated with carotid intima-media thickness, epicardial adipose tissue thickness, left ventricular mass, and left ventricular mass index and was found to be an independent predictor for epicardial adipose tissue thickness and carotid intima-media thickness, carotid intima-media thickness and epicardial adipose tissue thickness values showed a distribution in a higher scale the same body mass index range in children of mothers with maternal obesity and gestational diabetes mellitus.

Increased insulin in obese individuals increases left ventricular mass by increasing blood pressure by way of sympathetic nervous system activation and renal reabsorption of sodium.[26] Similar to our study, research by Litwin et al. states that left ventricular mass was only affected by children's body mass index , and both left ventricular mass and left ventricular mass index were independent of maternal obesity, weight gain, and diabetes.[27]

Arterial distensibility and strain were found to be reduced, and stiffness was found to be increased in our study group. This finding supports that hyperinsulinism occurring in presence of gestational obesity or gestational diabetes, oxidative stress and inflammation lead to disruption in vascular structure and functions. Increased insulin and C-peptide levels in blood samples obtained from the umbilical cord in babies of diabetic mothers and increased thickness in the umbilical artery intima-media layer confirm that vascular alterations begin in the intrauterine life.[28] The negative correlation between waist circumference and arterial distensibility and strain in children of mothers with gestational diabetes mellitus supports that inflammatory cytokines released from increased adipocytes cause negative effects on vascular elasticity and compliance by leading to endothelial dysfunction, and triggering atherosclerosis.

Even though previous studies have emphasised that SGA (small gestational age) birth or premature birth could lead to adverse effects on cardiac remodelling and vascular structures,[29] any significant difference between preterm and term-born children is not determined in our study in terms of subclinical atherosclerosis parameters. It can be thought that this may be due to the fact that the number of preterm birth cases is quite low (16) compared to the number of term birth cases (62).

Unconscious and poor nutrition is more common in families and populations with poor socio-economical status. The fact that the study group had a lower education level and higher body mass index values supports that low education level and low socio-economical status increase the risk for obesity and metabolic syndrome.[30]

The lower education level of the mothers in the study group and higher body mass index values in the children compared to the control group indicate that the risk was increased not only for maternal obesity but also for obesity in the children. Adult and paediatric studies showed that deterioration in education and economical status caused an increase in blood pressure, carotid intima-media thickness, and arterial stiffness.[31,32] It is thought that economic trouble and lack of education lead to an increase in catecholamine and cortisol levels by triggering stress factors, influence cardiac structure, and functions, and cause a reduction in vascular compliance and elasticity, and an increase in stiffness by triggering endothelial dysfunction.[31,32] The findings that arterial distensibility and strain were higher, and stiffness was lower in the children whose mothers had gestational diabetes mellitus and a high family income compared to the ones with a low family income; and that left ventricular mass and left ventricular end-diastolic internal thickness were higher in the children whose mothers were unemployed and had obesity compared to the children whose mother were employed in our study, again supported these studies.

Despite the rate of practicing exercise being significantly higher in the mothers in the control group compared to the study group, no impact of this result was found on the children's cardiac

https://doi.org/10.1017/S1047951122002402 Published online by Cambridge University Press

functions and subclinical atherosclerosis markers. We think that this result might have arisen from irregular and ineffective exercise.

Conclusion

Our study is the first to include such comprehensive parameters in a single study, in which both maternal obesity, gestational diabetes mellitus, and control groups were investigated simultaneously. Our study showed that low socio-economical status was related to the risk of gestational diabetes mellitus or maternal obesity; hence, this increased the risk of obesity in children, influenced the development of insulin resistance, and caused lipid profile disturbances. Even though atherosclerosis subclinically begins in childhood, maternal obesity or gestational diabetes mellitus was observed to contribute to the development of atherosclerosis in children. Weight gain and inadequate glycaemic control during pregnancy influence maternal health negatively as well as leading to a risk for cardiovascular disease at advanced ages in children and in generations to come. Therefore, preventive strategies in terms of obesity and diabetes during gestational follow-up may provide a better future for both mothers and children in terms of cardiometabolic aspects.

Limitation

One of the limitations worth stating about our study is the relatively small number of samples. The study was designed just before the COVID-19 pandemic and was carried out under the pandemic conditions; hence, the number of healthy patients remained below those who applied to the outpatient clinic, and therefore the number of volunteer participants. Another limitation that can be discussed is fathers were not involved in the study. It has been shown in previous studies that cardiometabolic conditions of the children are affected by fathers also.[19] In this respect, the inclusion of fathers in the study may be a light for potential future studies. The most crucial and strong aspect of our study differs from existing studies is that it is a large-scale study showing the effects of gestational diabetes and maternal obesity, as well as the effects of sociocultural and economic levels on the children's cardiovascular health.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S1047951122002402

Acknowledgements. None.

Financial support. This research received no specific grant from any funding agency, commercial, or not-for-profit sectors.

Conflicts of interest. None.

Ethical standards. The study was conducted in accordance with the Helsinki Declaration, and written informed consent was obtained from the parents in the study and control groups.

References

1. Iessa N, Bérard A. Update on prepregnancy maternal obesity: birth defects and childhood outcomes. J Pediatr Genet 2015; 4: 71–83.
2. Akcakus M, Koklu E, Baykan A, et al. Macrosomic newborns of diabetic mothers are associated with increased aortic intima-media thickness and lipid concentrations. Horm Res 2007; 67: 277–283.
3. Santangeli L, Sattar N, Huda SS. Impact of maternal obesity on perinatal and childhood outcomes. Best Pract Res Clin Obstet Gynaecol 2015; 29: 438–448.
4. Lamotte C, Iliescu C, Libersa C, Gottrand F. Increased intima-media thickness of the carotid artery in childhood: a systematic review of observational studies. Eur J Pediatr 2011; 170: 719–729.
5. Cabrera-Rego JO, Iacobellis G, Castillo-Herrera JA, et al. Epicardial fat thickness correlates with carotid intima-media thickness, arterial stiffness, and cardiac geometry in children and adolescents. Pediatr Cardiol 2014; 35: 450–456.
6. Yuan WL, Lin J, Kramer MS, et al. Maternal glycemia during pregnancy and child carotid intima media thickness, pulse wave velocity, and augmentation index. J Clin Endocrinol Metab 2020; 105: e2581–e2590.
7. Sundholm JKM, Litwin L, Rönö K, et al. Maternal obesity and gestational diabetes: impact on arterial wall layer thickness and stiffness in early childhood - RADIEL study six-year follow-up. Atherosclerosis 2019; 284: 237–244.
8. Davies GAL, Maxwell C, McLeod L. No. 239-obesity in pregnancy. J Obstet Gynaecol Can 2018; 40: e630–e639.
9. Neyzi O, Bundak R, Gökçay G, et al. Reference values for weight, height, head circumference, and body mass index in turkish children. J Clin Res Pediatr Endocrinol 2015; 7: 280–293.
10. Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics 2017; 140: e20171904.
11. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents.Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics 2011; 128: S213–56.
12. Zimmet P, Alberti KG, Kaufman F, et al. The metabolic syndrome in children and adolescents - an IDF consensus report. Pediatr Diabetes 2007; 8: 299–306.
13. Metwalley KA, Farghaly HS. Subclinical hypothyroidism in children: updates for pediatricians. Ann Pediatr Endocrinol Metab 2021; 26: 80–85.
14. Khoury P, Mitsnefes M, Daniels S, Kimball T. Age-Specific Reference Intervals for Indexed Left Ventricular Mass in Children. Journal of the American Society of Echocardiography 2009; 22: 709–714.
15. Stein JH, Korcarz CE, Hurst RT, et al. Use of carotid ultrasound to identify the subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr 2008; 21: 93–190.
16. Lacombe F, Dart A, Dewar E, Jennings G, Cameron J, Laufer E. Arterial elastic properties in man: a comparison of echo-Doppler indices of aortic stiffness. Eur Heart J 1992; 13: 1040–1045.
17. Chandler-Laney PC, Bush NC, Rouse DJ, et al. Maternal glucose concentration during pregnancy predicts fat and lean mass of prepubertal offspring. Diabetes Care 2011; 34: 741–745.
18. Namazi N, Djalalinia S, Mahdavi-Gorabi A, et al. Association of wrist circumference with cardio-metabolic risk factors: a systematic review and meta-analysis. Eat Weight Disord 2020; 25: 151–161.
19. Gaillard R, Steegers EA, Duijts L, et al. Childhood cardiometabolic outcomes of maternal obesity during pregnancy: the generation R study. Hypertension 2014; 63: 683–691.
20. Regnault N, Kleinman KP, Rifas-Shiman SL, Langenberg C, Lipshultz SE, Gillman MW. Components of height and blood pressure in childhood. Int J Epidemiol 2014; 43: 149–159.
21. Torun E. Subclinical hypothyroidism in obese children. Dicle Medical Journal 2013; 40: 5–8.
22. Michalaki MA, Vagenakis AG, Leonardou AS, et al. Thyroid function in humans with morbid obesity. Thyroid 2006; 16: 73–78.
23. Berenson GS, Srinivasan SR, Bao W, et al. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The bogalusa heart study. N Engl J Med 1998; 338: 1650–1656.
24. Santos S, Monnereau C, Felix JF, et al. Maternal body mass index, gestational weight gain, and childhood abdominal, pericardial, and liver fat assessed by magnetic resonance imaging. Int J Obes (Lond) 2019; 43: 581–593.
25. Iacobellis G, Assael F, Ribaudo MC, et al. Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction. Obes Res 2003; 11: 304–310.

26. Insulin Direnci Calistay Raporu [Internet]. Turkdiab.org. 2017 [cited August 2017]. Available from: https://www.turkdiab.org/admin/PICS/webfiles/Insulin_Direnci_Calistayi.pdf.
27. Litwin L, Sundholm JKM, Rönö K, et al. Transgenerational effects of maternal obesity and gestational diabetes on offspring body composition and left ventricle mass: the Finnish Gestational Diabetes Prevention Study (RADIEL) 6-year follow-up. Diabet Med 2020; 37: 147–156.
28. Tam WH, Ma RC, Yip GW, et al. The association between in utero hyperinsulinemia and adolescent arterial stiffness. Diabetes Res Clin Pract 2012; 95: 169–175.
29. Bassareo PP, Fanos V, Puddu M, et al. Epicardial fat thickness, an emerging cardiometabolic risk factor, is increased in young adults born preterm. J Dev Orig Health Dis 2016; 7: 369–373.
30. Wamala SP, Lynch J, Horsten M, et al. Education and the metabolic syndrome in women. Diabetes Care 1999; 22: 1999–2003.
31. Thurston RC, Matthews KA. Racial and socioeconomic disparities in arterial stiffness and intima media thickness among adolescents. Soc Sci Med 2009; 68: 807–813.
32. Liu RS, Burgner DP, Sabin MA, et al. Childhood Infections, socioeconomic status, and adult cardiometabolic risk. Pediatrics 2016; 137.

https://doi.org/10.1017/S1047951122002402 Published online by Cambridge University Press